Clostridium Difficile Infection in the Hematopoietic Unit: A Meta-Analysis of Published Studies

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A B S T R A C T

Hematopoietic stem cell transplant (HSCT) recipients are at high risk of contracting *Clostridium difficile* infection (CDI). We systematically searched the PubMed and EMBASE databases through March 2014 and performed a random-effects meta-analysis to estimate the prevalence and trends of CDI over time. Among 48 eligible articles that included 12,025 patients at risk, we estimated that 7.9% (95% confidence interval [CI], 6.5% to 9.5%) of HSCT patients are diagnosed with CDI during the peri-transplantation and late post-transplantation periods, an estimation that is relatively consistent across studies ($\tau^2 = .032$). Prevalence of CDI is significantly higher among the 5120 allogeneic patients (9.3% [95% CI, 7.0% to 11.9%]), compared with the 4665 autologous patients (5.2% [95% CI, 3.8% to 6.9%]) ($P = .02$), and as many as 1 of 10 allogeneic transplant recipients are expected to be diagnosed with CDI compared with 1 of 20 autologous transplantation patients. However, this difference did not reach statistical significance when stratified data from the same centers were examined ($P = .11$). Importantly, we found an increasing trend of CDI diagnosis both worldwide ($P = .02$) and across studies conducted in North America ($P = .03$) over the last 34 years. Notably, studies with a follow-up period that extended through the late post-transplantation period (after day +100) had a similar prevalence of CDI as those that followed patients only during the peri-transplantation period (up to day +100) ($P = .94$). In summary, CDI is common in the hematopoietic transplantation setting and the majority of infections occur in the peri-transplantation period. The prevalence is almost 9-times higher than that reported among all hospital stays, with an increasing trend over time.

INTRODUCTION

Clostridium difficile is the most common cause of acute infectious diarrhea in the hospital setting [1]. Although the prevalence of other health care–associated infections seems to decline [2], the prevalence of *C. difficile* infection (CDI) has increased and has only recently reached a plateau [3]. Overall, the prevalence [4], morbidity, mortality [5], and medical care costs of CDI have reached historic highs [6], and the Centers for Disease Control and Prevention has categorized *C. difficile* as 1 of the 3 pathogens that are considered "urgent threats" [7].

Studies highlighting the significant prevalence of CDI among hematopoietic stem cell transplantation (HSCT) patients are increasingly published [8]. The susceptibility of this patient population to CDI can be attributed to the frequent and prolonged contact with the health care setting, as well as to the prolonged exposure to antibiotics. Also, the high degree of immunosuppression and graft-versus-host-disease (GVHD) appear to be independent predisposing factors among allogeneic transplant recipients, possibly by disrupting the colonic mucosa [9]. To study the epidemiology of CDI in the hematopoietic transplantation setting, we performed a systematic review and meta-analysis of published studies.

MATERIALS AND METHODS

Study Selection

We searched PubMed (1967 to March 2014) and EMBASE (1963 to April 2014) medical databases to identify studies that reported the prevalence of CDI among patients who receive hematopoietic stem cell transplantation. The concise search term was ([stem cell] OR marrow OR chord OR autologous OR allogeneic) AND transplant* AND (clostrid* OR difficile OR infect* OR diarrhea OR [clostridium difficile] OR [pseudomembranous colitis]). Potentially eligible articles by title and abstract reading were assessed in full text. The search was supplemented by reviewing reference lists of the eligible studies. We included in our analysis both published literature and abstracts from conference proceedings. The meta-analysis follows the Meta-analysis of Observational Studies in Epidemiology guidelines [10] (Supplementary Table S1).

Selection Criteria

Studies were considered eligible if they reported the prevalence of CDI among HSCT patients during their hospitalization after stem cell transplantation. A restriction for English literature was imposed.

Outcomes of Interest

The primary outcome of interest was the prevalence of CDI among HSCT patients. *CDI* was defined as diarrhea combined with a positive stool test result for the presence of toxigenic *C. difficile*. Prevalence was calculated as the proportion of patients diagnosed with CDI among patients "at risk," ie, HSCT recipients. A subgroup analysis was performed for geographical region, year of study conduction, autologous and allogeneic transplantation, duration of follow-up, and study design.

The *peri-transplantation period* was defined as the pretransplantation period, pre-engraftment period (approximately 0 to 30 days after transplantation), and postengraftment period (approximately 30 to 100 days after transplantation), whereas the *late post-transplantation period* was considered to be the period after day +100 of transplantation. The secondary outcome of interest was the *recurrence rate of CDI* in infected patients (defined as complete abatement of CDI symptoms while on appropriate therapy, followed by subsequent reappearance of diarrhea and other symptoms after treatment has been stopped).

Data Extraction

Two reviewers (I.M.Z. and P.D.Z.) independently evaluated studies that were considered for inclusion in the meta-analysis. Relevant information

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from the text, tables, and figures of eligible articles were extrapolated and summarized using a spreadsheet. Data from trials published in duplicate were included only once, and the maximum of relevant information was extracted. Consensus was reached if there were any discrepancies between the reviewers. The following data were extracted: first, we extracted the characteristics of each study, including the study design (prospective versus retrospective), the country of origin, and the study period. Second, information on the patient population, including underlying diagnosis, number of HSCT patients, source of stem cells, type of transplantation (autologous or allogeneic), number of *C. difficile*–infected patients, number of BI/NAP1/027 strains, and severity of CDI, was extracted. The severity of CDI was assessed using the CDI severity score, with low severity representing uncomplicated inpatient management without need for imaging; medium severity, the presence of colitis on imaging; and severe disease represented by evidence of sepsis, intensive care unit admission, surgery for colitis, or death due to colitis [11]. Finally, we extracted the information relevant to the follow-up, including the duration of follow-up and the number of recurrent episodes. To model the time trends of CDI among HSCT patients, an index year of each eligible study was determined. For this purpose, we used the year that the study was conducted and not the year of publication. If the study did not provide stratified data per year, a midyear was calculated.

Quality Assessment

Two reviewers (I.M.Z. and P.D.Z.) independently assessed the methodological quality of eligible studies using the Newcastle-Ottawa Quality Assessment Scale, which is a "star-based" rating-system [12]. According to the scale, studies were evaluated in the context of the representativeness of the exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, assessment of outcome, adequacy of follow-up time for outcomes to occur, and adequacy of follow-up of cohorts. Each study could receive up to 6 stars, as the fields "selection of the nonexposed cohort," and "comparability between cohorts" were not applicable for our meta-analysis. The study population was considered representative of the exposed cohort if CDI were reported among all available transplantation patients and not among a specific subpopulation. The follow-up time was deemed adequate for outcomes to occur if it were at least 100 days or if it included the whole period of hospitalization. Studies that received at least 4 stars were deemed of adequate quality to extract relevant data.

Data Analysis

The meta-analysis was performed using a random-effects model to estimate the pooled (combined) prevalence and the 95% confidence intervals (CI), using Der-Simonian and Laird weights [13]. To avoid an undue large weight for studies with low or high prevalence (prevalence close to 0 or 1), we used the Freeman-Tukey arcsine methodology [14]. Publication bias was assessed by Egger's test [15]. Statistical heterogeneity was assessed using the between-study variance τ^2 estimation [16], and subgroup and sensitivity analysis were used to account for possible sources of heterogeneity. For time trends, the estimated coefficients were retransformed to prevalence and fitted values were drawn against the index year [17]. Statistical analysis was performed by use of Stata v13 software package (Stata Corporation, College Station, TX). The significance threshold was set at .05.

RESULTS

Our initial literature search yielded 74,214 citations and the date of our last access to the databases was March 28, 2014. After scrutinizing the title and abstract of the retrieved citations, 132 articles were assessed in full text and 83 of these studies were excluded because they did not provide extractable data on the prevalence of CDI among HSCT patients. The remaining 49 studies were considered suitable for our analysis (Supplementary Appendix). Six studies contained partially overlapping data, and therefore the maximum of relevant information was extracted from each. Details for the selection process of eligible articles are presented in the flow chart (Supplementary Appendix).

The 48 included studies (coded from 49 articles) were published from 1982 to 2014 and reported data on 12,025 HSCT patients from 1980 to 2012. Data from the individual studies are presented in Supplementary Table S2. On the basis of the Newcastle-Ottawa scale, all studies were deemed of adequate quality to be included in the analysis (Supplementary Table S3). Twelve studies were prospective and 34 were retrospective, whereas 1 study contained both prospectively and retrospectively collected data and 1 did not report the study design. Among 48 included studies, 30 studies were conducted in North America, 12 in Europe, 4 in Asia, 1 in Australia, and 1 in South America.

The pooled prevalence of CDI among 12,025 HSCT patients from 48 studies was 7.9% (95% CI, 6.5% to 9.5%), an estimation that was relatively consistent among studies ($\tau^2 = .032$). Across the 30 studies conducted in North America, the estimated prevalence of CDI was 8.4% (95% CI, 6.8% to 10.2%), which was higher than, but not significantly different from the estimated prevalence among European studies (6.0% [95% CI, 2.8% to 10.3%], $P = .20$). There was no evidence of publication bias, according to the Egger's test both for the overall estimate as well as the estimate across studies conducted in North America (bias −.24, $P = .81$; bias −.15, $P = .88$, respectively). We also made a subgroup analysis based on the study design (prospective versus retrospective) and found that this factor did not alter significantly the estimated prevalence of CDI among HSCT patients ($P = .86$). Moreover, we stratified studies based on the duration of follow-up, namely follow-up during hospitalization or less than day +100 versus follow-up longer than day +100, and we did not find a significant difference in the reported prevalence of CDI ($P = .94$) (Table 1).

The index year of all eligible articles was used to study the trend of CDI over time. An increasing trend was observed over the years among all studies ($P = .02$) (Figure 1A) and among the studies that were conducted exclusively in North America ($P = .03$) (Figure 1B). Of note is that 2 studies (reporting data on 130 patients) did not report the time frame of the study and, therefore, they were not included in the modeling of CDI over time.

Twenty-four studies provided extractable data on 4665 autologous HSCT patients, whereas 24 studies reported relevant data on 5120 allogeneic HSCT patients. The prevalence of CDI among patients undergoing allogeneic transplantation was 9.3% (95% CI, 7.0% to 11.9%), which was significantly higher than the corresponding figure among autologous transplant recipients (5.2% [95% CI, 3.8% to 6.9%], $P = .02$). Among the 6 studies with ≥200 patients that reported stratified data on both autologous and allogeneic transplant recipients, the point estimate of CDI prevalence continued to be higher among allogeneic HSCT patients, but the estimated difference was not statistically significant (12.9% [95% CI, 6.9% to 20.4%] versus 7.1% [95% CI, 5.6% to 8.8%], respectively [$P = .11$]).

Thirteen studies provided data on episodes of recurrence among a total of 480 infected patients. Individual study data are presented in Supplementary Table S2. The reported recurrence rate across studies spanning the last decade ranged from 0 to 27%. However, as discussed below, the quality of data did not allow further analysis.

Six studies reported data regarding the severity of CDI among infected patients. Two studies did not report any severe cases of CDI among 16 and 53 infected patients and another 2 studies reported 1 episode of death each due to colitis out of 6 and 8 infected patients. Finally, 2 studies reported 1 severe CDI each that required intensive care unit admission (of 51 and 72 infected patients). Also, only 2 studies (both from Europe), which were published in 2012 and 2014, evaluated the prevalence of BI/NAP1/027 strain among the infected patients and neither of these studies

Table 1
Summary Estimates

C. Difficile Infections	Studies (arms)	N	Combined Effect (95% CI)	τ^2	*P* Value
All studies	48 (49)	12,025	7.9% (6.5%-9.5%)	.032	
Studies ≥200 patients	22	9628	6.6% (4.9%-8.5%)	.026	Ref.
Studies <200 patients	27	2397	9.7% (7.0%-12.8%)	.055	.08
Geographic region					
North America	30 (31)	9160	8.4% (6.8%-10.2%)	.024	Ref.
Europe	12	2186	6.0% (2.8%-10.3%)	.068	.20
Graft type	40 (49)				
Autologous	24	4665	5.2% (3.8%-6.9%)	.021	Ref.
Allogeneic	24	5120	9.3% (7.0%-11.9%)	.035	.02
Duration of follow-up					
During initial hospitalization	36	8505	7.3% (5.2%-9.7%)	.062	Ref.
Further follow-up	14	3856	7.1% (4.6%-10.1%)	.034	.94
Study design					
Prospective	13	1587	8.2% (4.9%-12.4%)	.049	Ref.
Retrospective	35	10,388	7.8% (6.2%-9.5%)	.030	.86

Ref indicates referent subgroup for comparison.

detected any BI/NAP1/027 strain of *C. difficile* in their study population. Finally, no study examined the impact of CDI on the length of hospital stay.

DISCUSSION

Hematopoietic transplant recipients are particularly vulnerable to *C. difficile* infection and an increasing number of retrospective and prospective studies are published to address this association [8]. Indeed, we found an overall prevalence of CDI of 7.9%, which is circa 9 times higher than what is reported in the general hospital population (.9% of all hospital stays in 2009) [3]. Importantly, we observed that hematopoietic transplant recipients are being increasingly diagnosed with CDI over the last 34 years. This trend remained significant when studies conducted exclusively in North America were examined and can reflect an actual change in *C. difficile* epidemiology because of the emergence of more virulent strains [5,18].

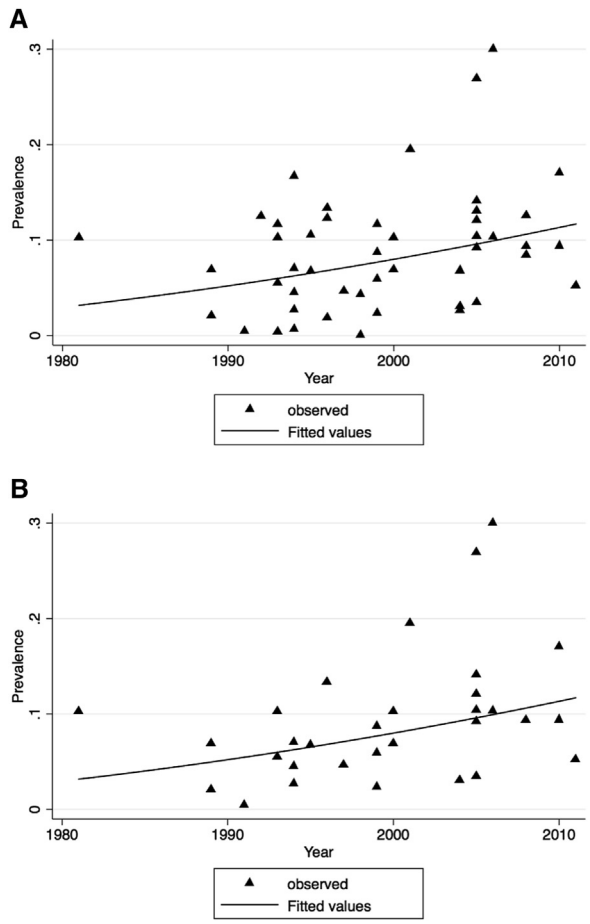

Figure 1. Prevalence of CDI over time. (A) Observed (triangles) and fitted (line) CDI prevalence estimates (all studies), by study midyear. (B) Observed (triangles) and fitted (line) CDI prevalence estimates, by study midyear, for studies conducted in North America.

In our analysis, we observed that approximately 1 of 10 allogeneic transplant recipients is diagnosed with CDI during the peri-transplantation and late post-transplantation periods, compared with 1 of 20 autologous transplant recipients, and this difference was statistically significant. Indeed, allogeneic transplant recipients are more prone to CDI than autologous HSCT patients and this difference has been attributed to the higher degree of immunosuppression, increased exposure to antibiotics, and disruption of bowel microbial ecology by GVHD [19,20]. However, the risk of developing *C. difficile* infection can be affected by several factors, such as regional epidemiology, time trends, and the use of different antimicrobial regimens for prophylaxis and treatment. To overcome these confounding factors, we separately analyzed large studies (over 200 patients) that provided stratified data on allogeneic and autologous transplantation patients. Again, allogeneic patients were more likely to be diagnosed with CDI, even though the difference in this comparison did not reach statistical significance ($P = .11$). Of note is that allogeneic transplant recipients may be more frequently investigated for diarrheal symptoms, and, therefore, there might be an increased possibility of identifying asymptomatic *C. difficile* colonization among this population [20].

The studies included in our meta-analysis had different follow-up protocols that ranged from 3 weeks to 2 years. Although, it is reasonable to assume that a longer the duration of follow-up is associated with a higher the number of identified CDIs, we did not find a significant difference in CDI prevalence between studies that followed patients only over the peri-transplantation period, compared with those that followed patients through the late post-transplantation period. This can be interpreted as an indication that the majority of CDIs occur in the peri-transplantation period (<100 days). That is reasonable, if we acknowledge that during this period patients are hospitalized for a prolonged

period of time, receive conditioning regimens and broad-spectrum antibiotics, and (relevant for allogeneic HSCT patients) suffer the effects of acute GVHD, which alters the normal colonizing gastrointestinal flora.

Of note is that newer diagnostic methods have been shown in prospective studies to be more sensitive in detecting toxins of *C. difficile* [21]. Therefore, the observed increasing trend of CDI might be, at least in part, the result of the increased sensitivity of molecular methods that are now more frequently used. We could not account for such a difference, as some of the available studies did not provide the exact method for detecting the toxin in stool, whereas others used more than 1 diagnostic method over the study period, without reporting stratified data on the prevalence of infections.

Recurrence is a common and challenging problem among *C. difficile*–infected patients and multiple studies have identified factors that can predict rate of recurrence [22,23]. The age of the patient, comorbid conditions, severity of the initial episode, and antibiotic used for its treatment, as well as re-exposure to antibiotics after successful treatment of the initial episode, are thought to be independent factors that can predict recurrence [24,25]. The recurrence rate reported in studies published over the last 10 years and included in our analysis varied from 0% to 27% (Supplementary Table S2). However, as the recurrence rate was a secondary outcome in all included studies, there was no concrete follow-up period after the initial episode and, thus, individual study data could not be pooled. Studies following *C. difficile*–infected HSCT patients for a concrete period of time are needed to specify the recurrence rate in this population, which has specific characteristics (younger age, increased exposure to antibiotics, immunosuppression) and to specify whether recurrent episodes are relapses of CDI or reinfections.

Meta-analyses are inherently subject to publication bias. To minimize this possibility, we included in our analysis both published studies as well as abstracts from conference proceedings published in EMBASE, and we used a broad search term to identify studies whose primary focus was not the prevalence of CDI, but the prevalence of other infections as well. Also, we performed the Egger's test, which yielded no evidence of publication bias. Moreover, we did not have enough data to draw valid conclusions regarding the impact of CDI in the outcome and length of hospital stay. Finally, prospective studies are more likely to be conducted in centers with a high prevalence of CDI and researchers might be prone to investigate episodes of diarrhea more thoroughly, compared with retrospective studies where data are collected from medical records. However, our estimated prevalence did not differ significantly between prospective and retrospective studies ($P = .86$).

CONCLUSION

HSCT patients constitute a highly vulnerable population for CDI, as our estimated prevalence of 7.9% is almost 9 times higher than the corresponding estimations for the general hospital population [3]. Moreover, our data do not support that the CDI has reached a plateau in this patient population and our finding that 1 of 10 allogeneic and 1 of 20 autologous transplant recipients are expected to be diagnosed with CDI during the peri-transplantation and late post-transplantation period highlight the need for prevention policies that apply to the specific characteristics of this population. It should be noted that information regarding the role of NAP-1 strain in this patient population, the severity and outcome of CDI, the rate of recurrence, and the impact of the infection in the length of hospital stay are not available from this study. Further, the impact of different diagnostic tests in the prevalence of CDI could not be determined, as no pertinent data could be extrapolated from the individual studies. Future studies should estimate the prevalence of the Nap1/BI/027 strain in this population and evaluate the impact of CDI among HSCT patients, and they should include monitoring for relapse and reinfection.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.06.001.

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Bortezomib for Refractory Autoimmunity in Pediatrics

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Therapy of refractory autoimmunity remains challenging. In this study, we evaluated the therapeutic effect of bortezomib, a proteasome inhibitor, by targeting plasma cells in 7 patients (median age, 9.9 years). Four doses of bortezomib were administered at a dose of 1.3 mg/m^2 intravenously (n = 6) or subcutaneously (n = 1) every 72 hours. Bortezomib was administered at a median of 120 days from laboratory confirmation of autoantibodies. All patients had failed 2 or more standard therapies. Rituximab was administered on the first day if B cells were present, and all patients received plasmapheresis 2 hours before bortezomib administration. Six patients experienced resolution of cytopenias. Two of 6 patients experienced recurrence of cytopenias after initial response. Adverse effects include nausea (n = 1), thrombocytopenia (n = 2), *Clostridium difficile* colitis (n = 1)), febrile neutropenia (n = 1), and cellulitis at the subcutaneous injection site (n = 1). Our experience suggests that bortezomib may be beneficial in the treatment of refractory autoimmunity in children.

INTRODUCTION

Autoimmune cytopenias occur as isolated events, as manifestations of various immune deficiencies, and are also a troublesome complication of allogeneic stem cell transplantation [1,2]. Autoimmune cytopenias are associated with significant morbidity, either attributed to the cytopenia alone or to the immune suppression required for its management [3,4]. The largest pediatric series of autoimmune hemolytic anemia after stem cell transplant estimated an incidence of about 6% and reported a high rate of mortality (53%) [5].

Current treatment for autoimmune cytopenias includes high-dose corticosteroids, intravenous immunoglobulin, rituximab, mycophenolate mofetil, and sirolimus [3]. Despite the availability of multiple therapeutic modalities, autoimmune cytopenias can be refractory to such treatments [3].

Aberrant production of autoantibodies by self-reactive plasma cells is an inherent characteristic of autoimmune diseases [6]. Findings show that long-lived plasma cells, refractory to immunosuppressant and B cell–depletion therapies, contribute to the maintenance of humoral memory and, in autoimmunity, to autoreactive memory [7]. Long-lived plasma cells can sustain chronic inflammatory processes in autoimmune diseases by continuously secreting pathogenic antibodies [6,7]. Proteasome inhibitors target plasma cells and effectively deplete this antibody-producing compartment [8]. Bortezomib has been used in refractory autoimmune diseases in adults and various case reports document successful treatments [9]. In addition, a case report of a patient with systemic lupus erythematosus and multiple myeloma describes the resolution of both disorders when treated with proteasome inhibition [10]. Reports have documented the success of bortezomib in treatment of anti-HLA antibodies and treatment of refractory acute cellular rejection in patients after a solid organ transplant [11-14]. In patients with antibody-mediated rejection after renal transplantation, bortezomib has successfully reversed the histologic changes and induced a reduction in donor specific anti-HLA antibody levels [15-17]. These reports have also demonstrated that bortezomib achieves this by depleting HLA-specific antibody producing plasma cells [18-20].

We hypothesize that autoimmune cytopenias become refractory because current therapies do not target autoreactive plasma cells, and outcomes can be improved with plasma cell agents. In this report we describe 7 children and

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